U.S. President Calls for AIDS Vaccine by 2007

Reaction Positive, but Questions Emerge About Specific Plans

by David Gold

While reaction to U.S. President Bill Clinton's call for development of an AIDS vaccine by the year 2007 was overwhelmingly positive, questions emerged as to what specific actions the United States and other industrialized nations intend to take to insure that rapid progress is made in HIV vaccine development.

In a speech at Morgan State University in Baltimore on 18 May, Clinton called for a commitment "to developing an AIDS vaccine within the next decade." He noted that meeting the goal "will take energy, focus and demand great effort from our greatest minds." The U.S. President also announced that a new AIDS vaccine research center would be established at the National Institutes of Health (NIH).

Over the past two years, IAVI has strongly supported a time-limited goal for development of an AIDS vaccine, along with G-7 leadership and greater industry investment in the development efforts. In testimony before the Presidential Advisory Council on HIV/AIDS in October, 1996, IAVI Interim President Seth Berkley called on President Clinton to "publicly challenge the nation and the world to a time-limited goal-oriented effort for an HIV vaccine by the year 2005" and to "call on other members of the G-7 to co-fund and co-support the effort."

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Report from the 9th Conference on Advances in AIDS Vaccine Development

(Editors' Note: This article was based on reports from Sam Avrett, David Gold and Peggy Johnston, Ph.D.)

On 4-7 May, 1997, more than seven hundred researchers came together at the campus of the National Institutes of Health, USA (NIH) in Bethesda for the Ninth Annual Conference on Advances in AIDS Vaccine Development, also known as the Meeting of the National Cooperative Vaccine Development Groups (NCVDG) for AIDS. The conference, sponsored by the U.S. National Institute of Allergy and Infectious Diseases (NIAID), is the world's largest regularly scheduled meeting on HIV vaccine-related research.

Overview

This year's conference was opened by presentations from Anthony Fauci, director of NIAID, David Baltimore, chair of the AIDS Vaccine Research Committee of the NIH, and Steve Wakefield of the AIDS Vaccine Advocacy Coalition. All three speakers agreed on several familiar themes: that multiple approaches are needed in vaccine research and development; progress toward a vaccine will be incremental; and that collaborative involvement by NIH, industry, international organizations and affected communities are crucial to the success of the effort.

In his talk, Fauci reviewed key NIAID strategies including support for basic research, preclinical product development, clinical research, and clinical trial readiness. In fiscal year 1998, NIAID will increase spending on AIDS vaccine research to 17.2 percent of the total NIAID AIDS research budget of US$678 million. However, vaccine research still constitutes less than 10 percent of overall NIH spending on AIDS research. Fauci also stated that he is

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Physical, financial and human resources for the center will be provided by both NCI and NIAID. While lab space will be sought in the vicinity of NIH, construction of a building on the NIH campus is being considered.

In terms of funding, the OAR has proposed a US$10 million budget for fiscal year 1998 for the new center. According to Paul, who first proposed the center, the budget allocation is “new funding” which will not be taken from other HIV-related research.

Lab Director to be Hired
In the view of many researchers, the ultimate success of the center will depend on who the NIH is able to attract as its director and the new resources that are provided. Gallo, a former NIH researcher himself, warns that “NIH is not filled with great vaccinologists.” He believes that the center’s success will be based on the person selected as director and the amount of authority that person is given.

According to Fauci, a search committee is being named to recruit a top level manager from the outside to head the center. The committee will conduct a broad nationwide search and will seek a director with “specific expertise in vaccine development.” The search will be fast-tracked and, in a best-case scenario, a director will be hired by fall.

NIH Director Harold Varmus appears to be actively involved in the overall effort and will head an executive committee that oversees the center. The AIDS Vaccine Research Committee, headed by David Baltimore, will be the scientific advisory committee to the center.

Questions also emerged as to the specific work that the center will undertake. NIH officials suggest that the lab will oversee everything from basic research to preparing pilot lots of candidate HIV vaccines. According to Paul, the center may have GMP (good manufacturing practices) and/or GLP (good laboratory practices) facilities, which would enable it to play a far greater role in producing candidate vaccines. To date, the NIH has relied almost exclusively on private industry to prepare candidate vaccines for Phase I trials.

Can a U.S. government agency conduct vaccine research and manufacturing in a rapid, timely, and efficient manner? “I certainly hope so,” says Paul.

Summit of the Eight Action
Clinton also vowed to “enlist other nations to join in a worldwide effort to find a vaccine.” These efforts, the U.S. President vowed, would begin at the Summit of the Industrialized Nations in Denver, Colorado.
To increase support for these efforts, IAVI organized an “International Call for Action on HIV Vaccine Development.” The declaration, which attracted the support of 68 leading AIDS organizations from 25 different nations in little more than one week, called on the industrialized nations to support a global effort to develop safe and effective HIV vaccines for use throughout the world and to expand this effort to other international forums, including the G-77 nations. The full text of the Call for Action was submitted to the leaders of all participating countries at the summit (see page 12).

At the summit, which was held on 20-22 June, 1997, the participating nations agreed on a final communiqué which stated that “in the long term the development of safe, accessible, and effective vaccines against AIDS holds the best chance of limiting, and eventually eliminating the threat of this disease.” The participants added that “we will work to provide the resources necessary to accelerate AIDS vaccine research, and together will enhance international scientific cooperation and collaboration” and that “collaboration among scientists and governments in the developed and developing world and international agencies will be critical.” The communiqué concluded by calling on other states to join in the effort.

IAVI Interim President Seth Berkley voiced strong support for President Clinton’s efforts and the actions taken at the Denver Summit, but noted that they were only a start. “The real work in implementing these agreements has just begun,” Berkley stated. “It will take a global commitment of resources, leadership and goal-oriented multilateral efforts to insure that rapid progress is made in HIV vaccine development,”

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Recombinant Subunit Proteins

Little new data was presented to support or refute the popular hypothesis that oligomeric forms of envelope proteins are more likely to provide protection. Tom Van Cott of the Walter Reed Army Hospital reported that an oligomeric form of gp160, but not monomeric gp120, protected three of fifteen macaques from challenge with a nonpathogenic SHIV-HXB2. In addition, when two of the protected macaques were boosted with an oligomeric gp120 and then rechallenged with heterologous nonpathogenic SHIV, both remained protected. David Montefiori of Duke University also presented a study showing that a number of different subunit protein vaccines were able to protect macaques against challenge with a non-pathogenic SHIV. In addition, protection correlated with levels of neutralizing antibodies against the challenge virus. However, neutralizing antibodies induced by the vaccines, including an oligomeric 11lgp140, failed to neutralize primary isolates.

Marc Girard of the Pasteur Institute reported that macaques immunized with either HIV envelope (MN/LAI) or V3 lipopeptides were not protected from challenge with pathogenic SHIV (89.6F) despite the presence of strong neutralizing antibodies to HIV (MN).

DNA Vaccines

A number of studies were presented on the immunogenicity of different DNA vaccine constructs. New data suggests that these vaccines can elicit potent CTL response and that these CTL responses can be enhanced. However, many DNA vaccines still appear to be weak in producing broadly neutralizing antibody and no new data was presented showing either animal protection or CTL killing of cells infected with heterologous virus.

DNA vaccination of pregnant chimpanzees can induce significant anti-HIV immune responses in newborns, according to data presented by Mark Bagarazzi of the University of Pennsylvania. Bagarazzi reported that pregnant chimps given HIV-DNA vaccine constructs produced antibodies to HIV, transferred significant levels of these antibodies to their healthy newborns and produced antibody (anti-env IgA) in their milk. Measurable HIV-specific CTL responses were also seen in the newborns.

Jong Kim, also of the University of Pennsylvania, presented a study showing that DNA vaccines that express co-stimulatory molecules could significantly increase HIV-specific cellular responses. Related posters from this research team, which is working with Apollon, Inc., a U.S.-based biotechnology company, included data on a DNA vaccine containing a number of HIV genes that is currently in animal studies. (Human studies of this vaccine should begin at four U.S. sites by August, 1997.) Data was also reported on a Phase I trial of a therapeutic DNA vaccine being tested for safety and immunogenicity in HIV-infected individuals.

A presentation by Margaret Liu of Merck & Co. provided additional information about the company's ongoing HIV-DNA vaccine program. Liu reported that multiple immunization of macaques with an HIV-DNA vaccine (encoding env) and a gp160 recombinant envelope boost, generated anti-envelope CTL responses and protected against challenge with a non-pathogenic SHIV.

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A number of adjuvants and cytokines are being studied for their ability to increase the immunogenicity of DNA vaccines. Researchers at the University of Massachusetts Medical Center and Aquila Biopharmaceuticals of Worcester, Massachusetts (USA) reported that injecting mice subcutaneously with the adjuvant QS-21 and a DNA vaccine (encoding for gp120) could generate nine-fold higher levels of antibodies than the DNA vaccine alone.

Another poster presentation examined the use of various cytokines to modify the immunogenicity of DNA vaccines. Researchers from the Karolinska Institute and the Yokohama University School of Medicine evaluated a DNA vaccine (containing the HIV genes env and rev) with a number of different expression plasmids encoding cytokines. Of the cytokines used, interleukin-12 (IL-12) and IL-2 increased CTL response, while IL-4 and alpha interferon improved antibody responses.

A unique approach to DNA immunization is to create libraries of fragments of HIV genes and to express them in DNA vaccines. Stephen Johnston of the Southwestern Medical Center gave an update on this approach. Johnston reported that by fragmenting the gag gene, new CTL epitopes were identified, which, if it is hoped, will elicit stronger CTL responses. To explore this strategy further, libraries of fragments from HIV-1 and HIV-2 were then created and inoculated into baboons. One group of these baboons also received cytokine adjuvants (GMCSF and IL-12). Antibodies to gag, pol, nef and the CTLs to gag were observed. If Johnston’s approach can successfully protect primates, it is likely to attract far greater attention.

A poster from Christopher Locher of the University of California at San Francisco (working with Stephen Johnston) reported that an HIV-2 DNA vaccine based on HIV-2 expression libraries induced an antibody response to gag and pol after only one immunization.

Genetically attenuated, or "mutant", SIV DNA may hold promise as a vaccine, according to a report by Larry Arthur, of the National Cancer Institute. The SIV vaccine contains a mutation that results in production of non-infectious particles. Arthur inoculated five macaques with mutant SIV DNA. None of the monkeys showed signs of productive SIV infection. As a control, four animals were vaccinated with plasmid DNA containing no SIV genes. Upon challenge, the four control animals all had high levels of SIV, whereas four of the five vaccinated monkeys had reduced or undetectable levels of virus.

Lipid-based delivery formulations of DNA vaccines can induce strong antibody and CTL responses in mice, according to a report by Susan Gould Fogerite of UMDNJ-New Jersey Medical School. Fogerite reported that lipid-based carriers, known as "cochleates", can deliver significantly higher levels of DNA plasmid into the body, thus requiring less actual DNA to be used. In addition, cochleate-based vaccines can be administered orally. The cochleate technology is licensed to Wyeth-Lederle Vaccines and a small study of the technology has been recently initiated in monkeys.

Live-Attenuated Vaccines

Studies continue to show that live-attenuated SIV vaccines can protect against pathogenic SIV by preventing disease progression. There was much discussion about conducting additional safety studies of these vaccines in animals (see IAVI Report, vol. 2, no. 1). Such tests could include multiple transfer experiments to evaluate whether the vaccines could revert to pathogenic virus and explore whether particular subpopulations may be unable to control the attenuated vaccine virus. In addition to safety studies, efforts to determine the correlating protection from live-attenuated SIV vaccines are being conducted by researchers in many parts of the world.

In an effort to develop live-attenuated vaccines with even better safety profiles, researchers at the University of California at Davis, led by Tilhuan Y Lima, deleted the SIV nef gene and replaced it with a gene expressing gamma interferon. Y Lima reported that, in comparison to the nef-deleted and triple-gene deleted SIV vaccines, the new construct generated lower levels of SIV in monkeys. In addition, he suggested that, unlike other live-attenuated vaccines, high doses of the gamma interferon vaccine appear

HIV Clades May Be Irrelevant to Vaccine Design  by Peggy Johnston, Ph.D.

A number of reports, presented at the NCVDG meeting and elsewhere, suggest that it might be possible to design an HIV vaccine that has wide use against many (and perhaps all) HIV-1 genetic clades (or subtypes).

While the correlates of immune protection against HIV remain unknown, most immunologic measurements in recipients of experimental vaccines have focused on neutralizing antibodies (Ab) and cytotoxic T lymphocytes (CTLs). Neutralizing Ab are thought to be important in blocking infection of cells by free virus particles. CTLs are believed to be important in eliminating HIV-infected cells. Since HIV exists in both cell-free and cell-associated forms in infected individuals, many believe that both Ab and CTL responses will be necessary to achieve protection, although there is clearly no consensus on this point.

To date, candidate HIV vaccines have been able to generate antibodies capable of neutralizing only laboratory strains of HIV based on the same clade as the vaccine (homologous virus). These results suggest that vaccines would have to be made from the HIV clade circulating in the target population.

However, there are rare antibodies from infected individuals that neutralize primary isolates of different HIV clades. In addition, studies of newer vaccine designs, such as complexed or oligomeric forms of envelope, suggest that alternative methods of presenting the HIV envelope to the immune system might lead to more broadly reactive antibodies. Until such methods are worked out, it will remain important to base antibody-inducing vaccines on local subtypes.

Until recently, data on the ability of HIV-specific CTLs from one clade to kill cells infected with a different clade of HIV has not been available. However, at the NCVDG meeting, Huyen Cao of Massachusetts General Hospital presented data demonstrating that CTLs from individuals infected with clade B HIV killed cells infected with a number of different HIV clades, including A, C and G from Africa. In addition, CTLs from individuals infected with non-clade B HIV frequently killed cells infected with clade B virus. Similar results
to be non-pathogenic in newborns. Upon challenge with pathogenic SIV, protection was only seen in the newborn which had developed high levels of SIV antibodies.

Researchers from the Aaron Diamond AIDS Research Center (ADARC) and the Walter Reed Army Hospital each reported that a monkey immunized with a live-attenuated SIV vaccine has developed signs of immune deficiency from the vaccine. According to Ruth Connor of ADARC, data from 20 macaque monkeys given the nef-deleted SIV vaccine suggests that vaccinated monkeys suppress challenge virus as early as five weeks after immunization. Full protection occurs in 10 to 15 weeks. Connor also reported that while 19 of the 20 vaccinated monkeys have undetectable levels of the nef-deleted virus, one monkey has detectable virus that is increasing in a pattern similar to that seen with simian AIDS. Mark Lewis of Walter Reed also reported that a monkey immunized with a nef-deleted vaccine developed AIDS from the vaccine.

New Monoclonal Antibody

Carl Hanson of the California Department of Health in Berkeley gave an unscheduled talk on a monoclonal antibody (named B4) being developed by United Biomedical, Inc. of Hauppauge, New York. The antibody is directed against the complex formed by the interaction between CD4 and the chemokine receptor, CCR5. The monoclonal antibody was able to neutralize primary isolates of HIV, as well as HIV-2, SIV and SHIV. Moreover, HIV was inhibited even when the antibody was added up to 24 hours after infection of cells. In addition, the monoclonal antibody protected SCID mice from challenge with HIV when it was administered four hours after challenge. Hanson also reported that this monoclonal antibody was non-toxic to cells. He suggested that B4 could be used for post-exposure prophylaxis and that a possible vaccine approach would be to try to elicit the same antibody specificity with a candidate vaccine.

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have been reported by others, including Bob Bollinger of the Johns Hopkins University in Baltimore, and Frances Gotch of the Chelsea and Westminster Hospital in London.

Perhaps most promising is that uninfected individuals who received ALVAC205, a recombinant canarypox expressing env, gag and pol, developed CTLs that could kill cells infected with HIV from different clades, albeit at lower levels than found in HIV-infected individuals. Only about half of the vaccine recipients developed measurable CTLs. Further, it is not known if individuals with different HLA types will produce broadly cross-reactive CTL in response to a clade B vaccine. A Phase I trial slated to start in Uganda will be the first attempt to begin to answer this question.

Are CTLs a determinant of immune protection, and, if so, might a vaccine that is broadly protective in some fraction of recipients already be in hand? Only expanded trials will be able to answer this question. A phase II trial of this vaccine has just been initiated in the U.S. ◆

Reports Suggest that Antibodies to Goat Virus “Neutralize” HIV

by David Gold

Among the more talked about presentations at the NCVDG Meeting was a report by University of Southern California (USC) researcher Angeline Douvas that a goat virus, which appears to be harmless to humans, may protect against HIV infection. According to Douvas, humans infected with novel variants of a virus known as caprine arthritis encephalitis virus (CAEV) often develop antibodies capable of neutralizing HIV.

Like HIV, CAEV, is a lentivirus. It is extremely common in goats and can cause a broad range of illnesses in these animals. However, humans, who are usually infected with CAEV by ingesting raw goat milk, do not appear to get sick from the virus.

CAEV viruses were first identified in humans diagnosed with mixed connective tissue disease (MCTD), an immune deficiency that causes symptoms similar to lupus. But according to Douvas, CAEV is not connected to MCTD.

In Mexico, up to 40 percent of children in some areas are infected with a CAEV-related virus. It is not certain whether humans can infect one another with the virus, but in lab tests, CAEV isolated from human plasma can infect cells from other humans.

Douvas first became interested in the potential for CAEV as an AIDS vaccine when she learned that some Mexican MCTD patients tested positive for HIV antibodies even though they were not infected with HIV. The USC researcher then found that CAEV antibodies were capable of “substantially neutralizing HIV-1.” In addition, Douvas has identified one patient who appears to be co-infected with CAEV and HIV. This patient reports that he has been HIV-positive for at least 15 years, without any apparent sign of immune suppression.

In her presentation, Douvas suggested that CAEV-related viruses could potentially be used as a live-attenuated AIDS vaccine. The immunity elicited by such vaccines could be increased by creating a combination CAEV/HIV or “chimeric” virus (CHIV).

Douvas told the IAVI Report that her lab has already developed a CHIV virus for testing in monkeys. They recently attempted to infect a monkey with CAEV and are monitoring the monkey biweekly to see if infection occurs.

Carl Dieffenbach, associate director of NIAID’s Basic Science Program, has been following the CAEV research closely from the beginning. He believes that the findings are “potentially very exciting.” However, Dieffenbach suggests that an important step for Douvas will be to “biologically characterize the apparent novel variants of CAEV in humans.” ◆
An Interview with David Baltimore

In December, 1996, David Baltimore, Ph.D., was appointed chair of the AIDS Vaccine Research Committee of the National Institutes of Health, USA (NIH). The committee was appointed by NIH Director Harold Varmus to provide advice on the NIH’s overall AIDS vaccine research program. As a researcher at the Massachusetts Institute of Technology, Dr. Baltimore was awarded a Nobel Prize in 1975 for his work on retroviruses. Dr. Baltimore has also served as president of Rockefeller University and was recently appointed president of the California Institute of Technology.

IAVI REPORT: It’s been six months since you became head of the NIH’s AIDS Vaccine Research Committee. Are you now more or less optimistic about prospects for an AIDS vaccine?

DAVID BALTIMORE: When I first contemplated the job, I was very unsure whether there was enough evidence to be optimistic. After looking at the research, I discovered that live-attenuated vaccines give pretty solid protection in monkeys. So, it seemed to me that if you could prevent AIDS in monkeys, there ought to be a way to do it in humans. That was six months ago and I haven’t changed that opinion. But I haven’t strengthened it either.

IAVI REPORT: What kind of progress has your committee made so far?

BALTIMORE: We’re getting up to speed about the research program and the elements that go into it. Our general philosophy is to encourage the pursuit of many different vaccine approaches without prejudicing any approach.

We’ve had a session on live-attenuated vaccines and we’re planning one on antibody response. And individual members are beginning to take on differentiated roles within the committee.

We want to get industry more involved in HIV vaccine development and to define their role in this effort. I have already met with researchers from Merck and Pasteur Mérieux Connaught and plan on meeting with other companies.

Our biggest effort so far has been to launch the Innovation Grants Program which is designed to fund important areas in HIV vaccine research. Three key areas of research have been identified. The program was set up in an extremely rapid time period and over 100 grant applications are now being reviewed. AmFAR (the American Foundation for AIDS Research) is running a similar grant program modeled on this.

IAVI REPORT: When will the Innovation Grants begin awarding funds?

BALTIMORE: This Fall. It’s on a very fast track. Six million dollars has been budgeted and that’s not the limit of resources that we can draw upon. We also plan to add new research categories in the future.

IAVI REPORT: President Clinton has made the development of an AIDS vaccine within ten years a national goal. How has this impacted your work?

BALTIMORE: By setting this goal, the President has helped raise the visibility of the issue. This will help us, along with the Innovation Grants, to attract new researchers to the field. But in 10 years, if we don’t have good candidate vaccines to put in clinical field tests then we really have to ask whether we can ever make a vaccine.

In 15 years of AIDS research, we have focused almost all our efforts on a very limited number of vaccine approaches. Some of these, we can now say pretty clearly, won’t get us anywhere. For example, most of the vaccines developed so far have been based on laboratory strains of HIV.

IAVI REPORT: It seems that from the beginning there has been tension between the so-called empiricists and so-called basic scientists. Why is that?

BALTIMORE: I’ve been trying to understand that as best I can. It’s one of the real learning curves for me. Everybody says empirical research is what gives you a vaccine. Well, it doesn’t give you anything else in science, so why should it give you an AIDS vaccine? Empiricism, as I understand it, is fundamentally research by analogy. It worked before so it’ll work again. But in science you don’t just try anything. You don’t go out and take protein off the shelf and start injecting people. There must be logic and reason behind it. When people defend the use of a gp120 vaccine developed from a laboratory strain they make scientific arguments about why this candidate vaccine might induce protective immunity in humans. Now, I think the bulk of the scientific community believes that a pure protein vaccine based on a laboratory strain is not going to protect humans, but it’s still a scientific argument that is being made.

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IAVI REPORT: Other programs outside NIH might have different approaches.

BALTIMORE: Yes. For example, the Department of Defense HIV vaccine program is run separately from the NIH. They make their own decisions. And that’s a good thing. I’ve always been very much in favor of pluralistic funding for research simply for that reason, because then different people can make judgments about what’s right and wrong and receive funding. In the end it’s proved out by the science.

IAVI REPORT: Let’s go through a couple of vaccine approaches. Will there be efficacy studies of the canarypox prime boost construct?

BALTIMORE: I really don’t know. A Phase II test is underway. It is actually designed somewhat differently than Phase I studies.
We're on a projectory to get higher levels of CTLs and better immune responses. Hopefully this study will give us more information about whether to initiate efficacy studies. But it's not a decision that our committee has been asked to make.

**IAVI REPORT:** In terms of HIV-DNA vaccines, how do we move research forward more rapidly?

**BALTIMORE:** This approach is actually moving forward quite rapidly. I've talked with researchers developing DNA vaccines in both commercial and academic laboratories. I visited the lab at Merck and they appear to have a very orderly and rational program in place. They want to get the best vector available and begin protection studies in monkeys.

**IAVI REPORT:** You've also spoken about the need to start looking more closely at traditional methods of vaccination.

**BALTIMORE:** That's correct. Almost all approved vaccines use either whole-inactivated or live-attenuated virus. It would be a mistake to abandon these approaches, without taking a very good and careful look at them. That is one of the responsibilities of our committee, to ensure that every reasonable approach is pursued. The term that has been used is to try to let a thousand flowers bloom.

**IAVI REPORT:** Do you think live-attenuated HIV vaccines will ever be tested in humans?

**BALTIMORE:** The issue is complicated. So far, we know that in monkeys given the attenuated virus, protection against disease has been extremely impressive. But there are real safety concerns. That is why the large safety trials in monkeys that IAVI is proposing are so important.

There is another possible approach. From what I hear, there is a cohort of Australians who received blood from a single donor and have become infected with what appears to be attenuated HIV. Researchers are now talking about modeling a vaccine on this attenuated virus. The rationale, as I understand, is that this virus has already been effectively tested and followed in humans for over 10 years. However, the safety questions may be so serious that people will not be prepared to go ahead with human studies of live-attenuated HIV vaccines.

**IAVI REPORT:** In terms of real dollars, is the U.S. government spending enough money on AIDS vaccine research?

**BALTIMORE:** At this point, I have not seen many very good ideas that are languishing for lack of funds. Resources are being increased at a reasonable rate. But we'll see how the Innovation Grants work. We may discover that there is a huge well of interest among very good people who have not been supported.

**IAVI REPORT:** How do you make sure that the private sector invests sufficient resources in HIV vaccine development?

**BALTIMORE:** I cannot say that I am satisfied with the level of investment in the private sector. We may need to provide some incentives for companies to ensure that multiple approaches are being pursued.

One company that has not yet spoken with us is American Home Products (Wyeth-Lederle Vaccines). They have funded research on HIV vaccines using adenovirus vectors and a study of this approach in chimpanzees was just published. I'd like to know whether the company plans to continue this research. If not, I think it's very important for the government to pick it up.

**IAVI REPORT:** What about fears that research funds for vaccines will come out of AIDS therapeutic or prevention research?

**BALTIMORE:** Well, our committee doesn't have any funds to allocate. That's the job of Bill Paul, Tony Fauci and Harold Varmus. And they have said consistently that money for vaccines will not come from existing programs. Recently, vaccine research has seen a greater increase, primarily because the base was so low. Of course, if we start doing efficacy studies a lot more money will be required. So, we're going to need to figure out what to do.

**IAVI REPORT:** The new NIH vaccine center is being overseen by a number of NIH institutes and committees. Is responsibility too diffuse for things to move quickly and efficiently?

**BALTIMORE:** I don't think that's fair. The resources for the lab are coming from two NIH institutes (NCI and NIAID), both of which have a good amount of vaccine expertise. The lab director will report to a committee headed by Harold Varmus (NIH Director), and my committee will serve as the scientific advisory board. What you must remember is that the climate of leadership at NIH is very different today. The reason it works so well is because Harold (Varmus) has made sure that the directors are working with each other. There's a real mutual respect.

It's a very different style and a real change. That's how we were able to get the Innovation Grants program set up so quickly.

**IAVI REPORT:** Is it important to have HIV vaccine development programs that compete with NIH efforts?

**BALTIMORE:** Absolutely. When you have a diversity of funding sources and research programs, the effort is much stronger. It goes to a very fundamental difference between the way science is done in the United States and abroad. Many countries have a Ministry of Science that tries to centralize scientific decision making and funding. In the United States we have scientific programs in many different government agencies, as well as in industry and the not-for-profit sector.

That means that if somebody has an idea and they send it to the NIH and the NIH says it's a lousy idea, that person can go to other funding sources. Many ideas are funded that way. And that's terrific, because it means that there is no orthodoxy. And it also keeps NIH more flexible because once NIH becomes too rigid or orthodox, there will be others to fund more innovative research.

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IAVI UPDATE

IAVI SAC Recommends Scientific Projects

IAVI's scientific advisory committee (SAC) met in March in Annecy, France to review funding proposals solicited by the Initiative and recommend the first set of scientific projects. The SAC also reviewed global progress on whole-killed and other particle-based HIV vaccine approaches. In its review of whole-killed vaccines, the SAC heard reports from John Oxford of the London Hospital Medical College, Martha Ebl of Immuno AG, Ron Moss of the Immune Response Corp. and Peter Salk of the Salk Foundation. The SAC concluded that whole-killed vaccines are a potentially viable approach to HIV vaccine development and that additional animal studies were needed to evaluate carefully prepared whole-killed products based on primary viral isolates. The committee also heard reports from Michel Klein of Pasteur Méruex Connaught (PMC) Canada and Hans Wolf of Regensburg University in Germany on studies of vaccine constructs using virus-like particles.

In its previous meeting, in November, 1996, in New York City, the SAC reviewed recombinant viral vectors. Speakers included Jean-Louis Exler of PMC, who presented an update on canarypox (ALVAC) vectors, Dennis Panicali of Therion Biologics, who reported on the company's attenuated vaccinia vector constructs, Andrew McMichael of Oxford University, who presented on recombinant modified vaccinia Ankara (MVA) and Norman Letvin of Harvard Medical School who summarized the status of other viral vectors including polio virus replicons, Venezuelan equine encephalitis virus, adenovirus and others. The committee concluded that the major gap in moving viral vectors forward into trial in developing countries was the absence of a boost capable of eliciting antibodies against non-subtype B clades of HIV. Should new information suggest which boost might be optimal, the SAC suggested that IAVI move to

ensure that such constructs progress rapidly into clinical studies. In addition, the SAC recommended that the National Institutes of Health (USA) be encouraged to conduct clinical studies that would allow for a direct comparison of different viral vectors (such as vaccinia and canarypox). Viral vectors, the committee concluded, appear to be moving forward, albeit slowly, and may require additional support at later stages in development. The SAC agreed to monitor this area and to consider targeted funding when appropriate.

IAVI Board Meets, Adds New Members

In a meeting in April, IAVI's board of directors approved the scientific projects proposed by scientific director Peggy Johnston and the SAC. The board authorized Johnston to initiate negotiations with the proposed recipients. Negotiations are ongoing with a goal of awarding initial funds by August of this year. In addition, two new members have joined the board: Shudo Yamazaki, director general, National Institute of Infectious Diseases (formerly National Institute of Health) of the Government of Japan and Geeta Rao Gupta, president of the International Center for Research on Women, Washington, D.C.

IAVI's International Advocacy Efforts Continue

In a letter to the more than 68 organizations in 23 nations that endorsed the "International Call for Action on HIV Vaccine Development," IAVI Interim President Seth Berkley noted that the Final Communiqué of the Denver Summit of the Eight contained a section on AIDS and accelerating AIDS vaccine development. "We all share satisfaction in this public commitment towards multilateral efforts in AIDS and vaccine development," Berkley wrote. "This, however, is only a first step. The next and more critical step will be to turn this political will into action," he added. IAVI is continuing to obtain organizational endorsements for the Call for Action.

NAT Becomes IAVI Partner

The National AIDS Trust (NAT) of the United Kingdom has become one of IAVI's partner organizations. As a partner, NAT will promote the need to support HIV vaccine development with the British government, private industry and community-based groups. The two organizations have worked closely in a series of international advocacy efforts. NAT's patron, Diana, Princess of Wales, endorsed the work of IAVI in a message of support for World AIDS Day last year, commending the "renewed global collaboration to find a long-term solution to HIV."

IAVI Report Goes Quarterly

With this issue, the IAVI Report will begin publication on a quarterly schedule. Since our launch one year ago, the IAVI Report has grown rapidly and is now distributed to individuals, organizations, and companies in more than 92 countries.

To be placed on our mailing list, send a request to: IAVI Report, c/o International AIDS Vaccine Initiative, 810 Seventh Avenue, New York, NY 10019, USA; e-mail: 103423.355@compuserve.com. The IAVI Report welcomes readers' comments and suggestions.

Report on AIDS Community/IAVI Consultations Available

In 1996, IAVI convened a series of meetings with AIDS community representatives from developing and industrialized countries to discuss specific concerns about HIV vaccine research and obtain advice on the future development of IAVI. A summary report of these meetings, edited by Doris Mugditchian, M.D., is now available. To obtain a copy, send a written request to: IAVI Interim Secretariat, 810 Seventh Avenue, New York, NY 10019, USA, or e-mail: 103423.355@compuserve.com.
AIDS in India: An Interview with Vulimiri Ramalingaswami

Vulimiri Ramalingaswami, M.D., D.Sc. is one of India’s leading AIDS researchers and president of the National Institute of Immunology in New Delhi. He has served as president of the Indian National Science Academy and chairman of the Global Advisory Committee on Medical Research of the World Health Organization. Dr. Ramalingaswami is also a member of IAVI’s scientific advisory committee.

IAVI REPORT: Can you tell us about the AIDS epidemic in India?
RAMALINGASWAMI: The epidemic is all over India. There are hot spots, where HIV infection rates are alarmingly high, like Mumbai (formerly Bombay), Madras, Maharashtra and Tamil Nadu.

Overall, an estimated two to five million Indians are now infected with HIV. If this estimate is correct then India is already the country with the largest number of HIV-infected persons in the world. And all this has happened since early 1986 when we discovered six prostitutes in Madras who were HIV-positive.

IAVI REPORT: Is there a significant AIDS-prevention effort in India?
RAMALINGASWAMI: AIDS is largely a disease of poverty in India. And what is being done is not very effective. For example, we need compulsory HIV testing of all blood products, so that transfusions cease to be a route of transmission. Legislation has been introduced, but no one will say that all the blood banks in India are providing HIV-tested blood.

The second line of attack is education about changing behavior and promoting condom use. But in India, unfortunately, there is a relatively low use of condoms. And on top of all this, there is a culture of silence that envelopes the AIDS problem.

IAVI REPORT: Are there discussions about initiating HIV vaccine trials in India?
RAMALINGASWAMI: Yes. A meeting was held in February, 1997, in Delhi, under the Indo-U.S. collaborative arrangements in health science (see box, page 10). That meeting has generated a great deal of interest in AIDS vaccines in India.

We now realize that no matter how spectacular the effects of triple drug therapy in the United States and other advanced countries, it does not touch the lives of Indians who are suffering from AIDS. In developing countries, where more than 90 percent of HIV infections occur, none of these drugs are available. And there is no way that these advances can be made available to all those in need. This is one of those tragic paradoxes today. The regimens can cost sixteen thousand dollars a year. With two to five million Indians infected with HIV, just imagine the cost.

And that’s where we come to the need for a vaccine.

Interest here in a vaccine is increasing. The National AIDS Research Institute in Pune is now developing a network for preventive HIV vaccine trials. They have spoken with Peggy Johnston (IAVI’s scientific director). Also, the two major government research agencies, the Indian Council of Medical Research and the Department of Biotechnology, are now actively working in the field of AIDS.

India has a critical mass of scientists, considerable scientific infrastructure and channels of public information, and ethical review mechanisms in place. Many vaccines are already being tested in this country, including a cholera vaccine and a leprosy vaccine. With these advantages, Indian researchers should get seriously involved in efforts to develop an HIV vaccine, possibly based on the C subtype, which is prevalent here and happens to be the most dominant subtype in the world.

India might participate in trials of vaccines made in different parts of the world, as long as rigorous standards for safety and manufacturing are utilized. Thailand and Uganda have already launched testing of vaccines based on subtypes not prevalent in their countries. They are gathering experience so if a vaccine based on a locally prevalent strain arrives, or other vaccines are effective across subtypes, definitive trials can be launched.

IAVI REPORT: Have you been following the controversy in Thailand over the gpl20 studies?
RAMALINGASWAMI: Not very much. All that I know is that the effectiveness of the gp120 vaccines, on their own, has not been established. Perhaps there is a question as to why it should be tried in Thailand, but one has to go very carefully into this.

Generally, there is a widespread suspicion, however unfounded it may be, that vaccines developed in advanced countries are only being tested in developing country populations. The term “guinea pigs” is used. That’s why Indian scientists must start working on developing their own products to test in this country. In this way we can overcome the blocks that have bedeviled vaccine trials around the world. We want to link up with IAVI and other parties to facilitate advancement of this goal.

IAVI REPORT: How do we address the fear in less developed countries about being used as guinea pigs in HIV vaccine trials?
RAMALINGASWAMI: We have to educate the public, the media, and community groups that India’s self-interest lies in such studies. At this time, we are not doing all we can to increase understanding of these issues.

We also have to balance the potential side effects with the enormous good that a vaccine can do. No technology can be 100 percent safe. So it’s these kinds of reflections that we need to work through. Indian scientists can play a role in conducting their own research and communicating through the media that it is now necessary to do HIV vaccine trials.

There is a trial going on in south India, near 

continued on page 10
Madras, using four different types of vaccines against leprosy. It is a vast, community-based study. And one of these vaccines comes from outside India.

**IAVI REPORT:** Will a vaccine tested in India have to be tested first in the industrialized country where it was developed?  
**RAMALINGASWAMI:** Yes, I think so.

If a vaccine developed in an industrialized country has shown some positive effect in different trials, there won’t be much of a problem in testing it in developing countries. But if vaccines have not yet shown a clear effect, different standards will be used. India has taken the stand that no vaccine developed in the industrialized countries can be tested in India without having first been tested in the population of the originating country.

But there could always be exceptions to that rule. For instance, if a product developed outside shows real promise, I would expect India to take an enlightened view and allow trials as long as the potential side effects are clear. The problem can be somewhat mitigated by creating expanded partnerships between groups like the World Health Organization, IAVI and developing countries to evaluate these ethical issues and move promising vaccines forward.

**IAVI REPORT:** Has there been any reaction to U.S. President Bill Clinton’s call for development of an AIDS vaccine within ten years?

**RAMALINGASWAMI:** I have not seen it highlighted in newspapers. In fact, there is very little public discussion about HIV vaccines. Stories that are printed are all hair-raising reports about the huge numbers of new infections in India.

Indian papers are now covering stories about the benefits of triple drug therapy. But people are hopeless and feel that these drugs will never be available in India.

**IAVI REPORT:** Are you concerned that if and when an effective HIV vaccine is developed, parts of the world that need it the most will have difficulty getting it?

**RAMALINGASWAMI:** This is a very good question. It is entirely possible. Because the vaccines in the childhood immunization program are low-cost and often subsidized, we have a mind-set that all vaccines are low cost.

But now, molecular biology and genetic engineering are becoming crucial to the development of modern vaccines. And these new vaccines may be very expensive. Therefore, developing and industrialized countries must begin working together so that pricing is kept in mind from the very beginning. There are ways in which high-priced drugs and vaccines can be sold to Third World countries at reasonable prices. Differential pricing systems, in terms of low income and high-income countries, and support from international organizations are both very important. We need to take steps from the beginning to make sure that what happened with HIV therapies does not happen with a vaccine.

**IAVI REPORT:** Finally, could you tell us how you ended up getting involved in AIDS vaccine research?

**RAMALINGASWAMI:** I am a pathologist and my interest has been in infectious diseases and immunity. When I became the head of the All India Institute of Medical Sciences, and later of the Indian Council of Medical Research, my interests widened. I first read reports about AIDS in the United States in the early ’80s and as the disease spread here, I got more deeply involved in research, advocacy and program development. I now focus a great deal of my time on AIDS, working with government agencies to stimulate and encourage research efforts.

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**Facts about HIV/AIDS in India**

- India is experiencing rapid and extensive spread of HIV. This is particularly worrisome since the country’s population of more than 900 million is greater than all of Africa, Australia and Latin America combined.
- There are an estimated 2 to 5 million people infected with HIV in India today, and 50,000 to 100,000 cases of AIDS may have already occurred in the country.
- The epidemic is spread primarily through heterosexual relations.
- The most rapid and well-documented spread of HIV has occurred in Mumbai (formerly Bombay) and the State of Tamil Nadu. In Mumbai, according to some studies, HIV prevalence has reached the level of 50 percent in sex workers, 36 percent of STD patients and 2.5 percent in women attending antenatal clinics.
- Certain regions, such as eastern India (Calcutta area) and northern India (New Delhi region), still show a lower prevalence of HIV (1 to 2 percent) among sex workers.
- Contrary to traditional belief, sexually transmitted diseases and sex with multiple partners are common in both urban and rural areas of India. An estimated 3 to 4 percent of some rural populations have a sexually transmitted disease.
- Many blood banks in India still do not screen blood for HIV before providing blood transfusions.
- Injection drug users is a problem in Manipur, which is in the North East region, where 55 percent of drug users are HIV-infected and one percent of women attending antenatal clinics are infected with HIV.
- HIV is rapidly spreading to rural areas through migrant workers and truck drivers. Surveys show that 5 to 10 percent of some truck drivers in the country are infected with HIV.
- An estimated 1 to 2 million cases of tuberculosis occur in India every year. In Mumbai, 10 percent of the patients presenting with tuberculosis are HIV-positive. Tuberculosis is the presenting symptom of AIDS in more than 60 percent of AIDS cases.

Indo-U.S. Meeting on HIV Vaccines
by Carole Hellman, Ph.D.

As part of an effort to more clearly define opportunities in AIDS vaccine research, development and testing in India, the Indo-U.S. Vaccine Action Program (VAP) sponsored a meeting in February of this year. Leading researchers from India, the United States, Uganda and Thailand participated in the meeting, which was held in New Delhi.

The VAP Program grew out of a U.S.-Indo Treaty designed to further cooperation between the two countries in health sciences, particularly in vaccine-related areas. The program is administered by a joint working group consisting of cabinet-level representatives from the U.S. Department of Health and Human Services and the Indian Ministry of Health, as well as the Indian Ministry of Science and Technology.

Overall, participants at the meeting, including key Indian scientists, concluded that India should enhance its role in the global effort to develop, evaluate, produce and introduce effective and appropriate HIV vaccines. According to Vimalini Ramalingaswami, President of the National Institute of Immunology in India, "the meeting has generated a great deal of interest in AIDS vaccines in India and other developing countries" (see interview, page 9).

Among the key recommendations of the meeting were:

- Ongoing efforts in HIV/AIDS surveillance in India should be expanded. The validation and standardization of assays used to detect HIV subtypes should also be expanded.

- India should fully integrate into the global effort to develop and test HIV/AIDS vaccines. It should consider the value of immediately embarking on Phase I vaccine trials using promising vaccine candidates to evaluate the importance of clade specificity and develop Indian expertise and leadership in the area.

- A national policy and plan of action is needed to foster the development and testing of HIV vaccines in India and increase public awareness about the benefits of such efforts.

- An HIV Vaccine Development and Testing Oversight Committee should be established to monitor long term safety, immunogenicity and efficacy issues.

- International collaboration should be fostered in the development of vaccine testing sites; subtype specific vaccines; product development capabilities; experimental animal models; indigenous diagnostic assay kits; and basic research opportunities, specifically in pathogenesis.

- Based on knowledge gained from Phase I vaccine trials, India should begin preparations to design and produce indigenous candidate vaccines most appropriate to India and to increase public and private support for such efforts.

Basic Science and Correlates of Protection Research

Mary Klotman of the Mount Sinai School of Medicine reported what may be a novel factor expressed by CD8 cells that can inhibit HIV. The presence of such a factor (other than b-chemokines) has long been proposed by University of California at San Francisco researcher Jay Levy. According to Klotman, the factor, named CAF10, can inhibit a number HIV strains including IIIB, BA-1 and primary isolates.

While a number of studies have suggested that HIV-specific cellular immune responses are found in seronegative partners of HIV-positive individuals, few have reported HIV-specific antibodies in such individuals. At the conference, Mario Clerici of the University of Milan reported that HIV antibodies (IgA) have been found in the cervical swabs and/or urine of 93 percent of HIV-exposed, seronegative individuals. In addition, he disclosed that when HIV peptides were added to the blood of HIV-exposed seronegative and HIV-positive individuals, higher levels of IL-2 and lower levels of IL-10 were seen in the exposed seronegative individuals.

In his presentation, David Baltimore shared his personal views that while the role of antibody remains unclear, he believes that CTL response may be more important for protection. In presenting results from his own lab, conducted in collaboration with Bruce Walker of Massachusetts General Hospital, Baltimore suggested a possible way in which HIV-infected cells avoid "clearing" by CTLs. Infection of cultured cells with HIV, he showed, downregulates MHC class I, making cells resistant to CTL killing. Downregulation of MHC was associated with the presence of the nef gene.

Summary

The conference demonstrated that an array of efforts are being made to discover how the human immune system might effectively prevent HIV infection or disease. However, definitive knowledge of the correlates of protection will most likely arise when the first (even partially) effective vaccine is identified. At this time, no Phase III efficacy studies have been initiated. Nevertheless, steady progress is being made in understanding the immunogenicity of several candidate vaccines in small animals and primates. In addition, promising new data suggest that at least one candidate vaccine is capable of generating HIV-specific CTL responses in humans and may have use against a broad number of HIV strains. Evaluation of this candidate in different populations is an important step. In addition, moving promising, novel designs into Phase I and then larger Phase II and III trials appears to remain a slow point in the development pipeline at this time.

Baltimore Interview continued from page 7

IAVI REPORT: Three years from now, how should we evaluate whether your efforts have been successful?

BALTIMORE: The central issue, three years from now, will be whether we have a more rigorous, broad-based research program that is looking at a wider range of approaches and candidate vaccines.

IAVI REPORT: You recently accepted the job of president of the California Institute of Technology (CalTech). Will you still be able to devote sufficient time to the AIDS vaccine position?

BALTIMORE: When I was interviewed by the trustees, the first question I asked was whether I would be able to continue with the commitment that I've made to the country and to the federal government in the area of AIDS vaccine research. They said they would consider it an honor for CalTech if I would continue this work.
International Call for Action on HIV Vaccine Development

On May 18, 1997, United States President Bill Clinton asked that we “commit ourselves to developing an AIDS vaccine within the next decade.”

AIDS has already taken the lives of millions of men, women and children. More than 29 million individuals have been infected with HIV. Each day, approximately 10,000 new infections occur; almost 95 percent of these in the developing world.

The investment of substantial government and private sector funds, over a sustained period of time, enabled researchers to make extraordinary progress in developing new HIV therapeutics.

Tragically, these advances are far beyond the reach of most HIV-infected individuals in the world. An effort of similar magnitude is needed to develop HIV vaccines, without which AIDS will continue its relentless march of destruction.

President Clinton stated that at the Summit of the Industrialized Nations in Denver, he will seek to “enlist other nations to join in a worldwide effort to find a vaccine to stop one of the world’s greatest killers.”

We, the undersigned, believe that HIV disease is a global disease and requires a global response. No single country or company has the resources to go it alone. Therefore, we call upon the industrialized nations of the world to support a global effort to develop safe, effective, preventive HIV vaccines for use throughout the world by 2007. We call upon the nations participating in the Denver Summit to agree on a specific plan to meet this goal.

We also call upon the large industrialized nations to devote new resources to this vaccine development effort, including assuring that vaccines are produced for developing countries, creating incentives for maximum participation of the pharmaceutical/vaccine industry, and agreement on specific mechanisms to ensure mutual cooperation and coordination of the effort. The excruciating burden of this disease demands that funds not be diverted from research for HIV therapeutics or prevention. The creation of new financing mechanisms, such as an AIDS Vaccine Development Fund and AIDS Vaccine Purchase Fund, should be considered.

Finally, we call upon the large industrialized nations to expand this effort to other international forums, including the G-77 nations. The industrialized nations must begin working with each other and less developed countries, private industry, international agencies, and non-governmental organizations to lay the groundwork for maximizing the research effort and securing broad international access to any HIV vaccines that are developed.

All countries around the world will gain by this effort and each has a unique contribution to make, such as providing funding, scientists, testing sites, and vaccine production. A global effort of this magnitude would demonstrate how the world can come together in an era of globalization for the good of all humankind - a noble goal for the next century.

ENDORSENG ORGANIZATIONS

Action Ciudadana Contra el SIDA (ACCSD), Venezuela; Agency for Cooperation in International Health, Japan; AIDS Action Baltimore, Inc., U.S.; AIDS Action Council, U.S.; AIDS Coordination Group, Netherlands; AIDS Education Global Information System (AEGIS), U.S.; AIDS Helpline NL, United Kingdom; AIDS Treatment News, U.S.; AIDS Vaccine Advocacy Coalition (AVAC), U.S.; Albert B. Sabin Vaccine Foundation, U.S.; All India Institute of Medical Sciences, India; Association against HIV/AIDS, Russia; Association de Recherche, de Communication et d’Action pour le Traitement du SIDA (ARCAFSIDA), France; Associazione Nazionale per la Lotta contro l’AIDS (ANLAI), Italy; British Medical Association, United Kingdom; British Medical Association Foundation for AIDS, United Kingdom; Center for AIDS Prevention Studies (CAPS), U.S.; Center for Vaccine Development, Mahidol University at Salaya, Thailand; Center of Research and Advanced Treatment in AIDS and HIV (CIATEAID), Mexico; Corporacion Chilena de Prevencion del Sida (CCPS), Chile; Deutsche AIDS Stiftung, Germany; EuroCASA Secretariat, Netherlands; European Public Policy Network on AIDS (EPNA), United Kingdom; Family Health Trust, Zambia; Fondation Marcel Merieux, France; Fundacao Osvaldo Cruz (FIOCRUZ), Brazil; Gay Men’s Health Crisis (GMHC), U.S.; Global AIDS Action Network (Gaan), U.S.; Global Network of People Living with HIV/AIDS (GNP+), U.S.; HIV Community Coalition of Metropolitan Washington, DC, U.S.; HIV/AIDS STD Activities in Bangladesh (HASAB), Bangladesh; Holistic Health Center, U.S.; Immigrants Fighting AIDS, U.S.; International AIDS Vaccine Initiative, U.S.; International Center for Research on Women, U.S.; International Christian AIDS Network (ICAN), United Kingdom; International Community of Women Living with AIDS (ICW), United Kingdom; International Council of AIDS Service Organizations (ICASO), Canada; International Council of Jewish Women, United Kingdom; International Lesbian and Gay Association, Belgium; International Union against the Venereal Disease and the Treponematoses, Australia; Jonas Salk Foundation, U.S.; Kenya National AIDS Control Programme, Kenya; Latino Comision on AIDS, U.S.; Liga Colombiana de Lucha contra el SIDA, Colombia; London Lighthouse, United Kingdom; Manathon of Mothers, U.S.; Mother’s Voices, U.S.; Mothers Organizing Mothers (MOMS), U.S.; National AIDS Fund, U.S.; National AIDS Trust, United Kingdom; National Association of People with AIDS (NAPWA), U.S.; National Lesbian and Gay Health Association (NLGHA), U.S.; Nederlandse Vereniging tot Integratie van Homoseksualiteit CCOH, Netherlands; Network of Self-Help HIV and AIDS Groups, United Kingdom; People with AIDS Health Group, U.S.; Project Inform, U.S.; San Francisco AIDS Foundation, U.S.; Scottish Voluntary HIV and AIDS Forum, United Kingdom; Southern Africa AIDS Information Dissemination Service (SAFIDS), Zimbabwe; St. Paul’s Trust Initiative for AIDS-free India, India; The Terrence Higgins Trust, United Kingdom; Title II Community AIDS National Network, U.S.; Treatment Action Group, U.S.; UCSF AIDS Research Institute, U.S.; Uganda Cancer Institute, Uganda; UK Coalition of People Living with HIV & AIDS, United Kingdom; Until There’s A Cure Foundation, U.S.; Vaccine Advocates, U.S.

IAVI is continuing to obtain organizational endorsements for this Call for Action. To sign on, call +1-212-377-2700, fax: +1-212-377-2727 or e-mail: 103423.355@compuserve.com. •

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